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BRIEF REPORT

Use of Infliximab to Treat Paradoxical Tuberculous Meningitis Reactions

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We documented dramatic responses to infliximab in 4 tuberculous meningitis cases with severe paradoxical reactions after effective antibacterial treatment, despite high-dose steroids. In every instance, infliximab was used as a last resort after all other options were exhausted, resulting in delayed initiation that may have adversely affected patient outcomes.

Keywords. infliximab; paradoxical reactions; tuberculous meningitis.

Tuberculous meningitis frequently results in permanent neurological sequelae [1, 2]. The characteristic inflammatory exudate at the base of the brain may block cerebrospinal fluid (CSF) flow with resultant hydrocephalus or cause cerebral ischemia and stroke secondary to vasculitis [1, 2]. Mass effects associated with localized inflammation may also compromise critical structures, such as the optic chiasm [3]. These effects may occur with natural disease progression or as a paradoxical reaction, generally defined as clinical worsening after initial improvement on appropriate antibacterial treatment.

Tumor necrosis factor (TNFα) is critical for effective host defense against mycobacteria, and monoclonal antibodies that inhibit TNFα, such as infliximab, greatly increase tuberculosis vulnerability [4]. On the other hand, deterioration of tuberculosis patients after infliximab cessation suggests that TNFα may also contribute to disease pathology [5]. The use of infliximab to control paradoxical reactions in a patient with tuberculous meningitis was first demonstrated in 2008 [6]. Subsequent case reports support the initial observations [7–10], but awareness of infliximab benefit in select cases is low and completely overshadowed by the perception of risk. Most clinicians remain highly reluctant to consider infliximab use in any tuberculosis patient.

We present a series of tuberculous meningitis cases with likely paradoxical reactions in whom infliximab was used with good effect. The Table 1 provides an overview of the case presentation, treatment, clinical progress, and outcome, with a focus on the administration and clinical effect of infliximab.

Case 1

A 36-year-old male bus driver who migrated to Australia from India 15 months prior was diagnosed with miliary tuberculosis and cerebral tuberculomas. Sputum, bronchoalveolar lavage (BAL), cerebrospinal fluid (CSF), and blood were all culture negative at the time. He was discharged home on isoniazid, rifampicin, pyrazinamide, ethambutol, and oral prednisolone. Interim brain magnetic resonance imaging (MRI) showed improvement of tuberculomas before readmission 6 weeks later with new-onset ataxia and drowsiness. Findings on the repeat MRI included hydrocephalus and cerebritis, with the patient experiencing rapid progression to coma requiring intubation and ventilation.

A brain biopsy was performed, and an external ventricular drain was inserted. The brain biopsy tested Xpert MTB/Rif positive, with rifampicin resistance detected. Empiric MDR treatment was commenced with moxifloxacin, amikacin, prothionamide, and linezolid added, awaiting culture results. Phenotypic drug susceptibility testing (DST) identified resistance to all first-line drugs with additional low-level resistance to moxifloxacin; line probe assays identified *katG*, *rpoB*, and *gyrA* mutations. First-line treatment, except pyrazinamide, was stopped, and the patient was continued on high-dose moxifloxacin with the addition of bedaquiline and clofazimine. On this regimen, the patient slowly improved and became more responsive, before deteriorating a second time with new midbrain tuberculomas, multiple infarcts, and increasing leptomeningeal enhancement on MRI.

In the absence of a clinical response to high-dose intravenous (IV) dexamethasone, a "trial dose" of infliximab was given. Fever and C-reactive protein (CRP) settled promptly, and the patient's sensorium improved within days, allowing him to be weaned off the ventilator. Symptoms recrudesced 3 weeks later, with new parenchymal foci and increased enhancement around existing

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Table 1. Tuberculous Meningitis Cases With Paradoxical Reactions Treated With Infliximab

Case	Diagnosis at Presentation	Site of Paradoxical Reaction	TB Treatment Regimen	Other Treatment Before and After Infliximab	Infliximab Dose	Outcome
Case 1: Flinders Hospital, Adelaide, 36 y, male HIV uninfected, India[a]	Miliary TB with TBM	Multiple brain tuberculomas and obstructed CSF flow with raised ICP	Empiric HRZE, then[c] high-dose mfx, amk, lzd[d], pto, Z, bdq, cfz	Before: High-dose steroids[b] for 3 mo After: High-dose steroids for 4 mo; tapered over 2 mo	10 mg/kg monthly x3	Rapid fever resolution with CRP decline; improved sensorium allowing weaning off the ventilator within days; long term—mild cognitive deficit, require assistance with activities of daily living
Case 2: Concord Hospital, Sydney, 32 y, female HIV uninfected, China[a]	Miliary TB with TBM	Multiple spinal tuberculomas with edema and local mass effect	Empiric HRZE, then[e] RZE + mfx	Before: High-dose steroids for 2 mo; decompressive spinal surgery After: High-dose steroids for 2 mo; tapered over 1 mo	5 mg/kg 0, 2, 6, and 14 wk	Rapid restoration of bladder function (2 wk) and mobility (3–4 wk); long term—full neurological recovery
Case 3: Royal North Shore Hospital, Sydney, 55 y, female HIV uninfected, Indonesia[a]	TBM and necrotic lymphadenitis	Multiple brain and spinal cord tuberculomas with cauda equina syndrome	HRZ + mfx	Before: High-dose steroids for 2 mo After: High-dose steroids for 4 mo; tapered over 2 mo; failed trial of thalidomide	5 mg/kg monthly x3	Rapid resolution of fever and meningism; improvement in lower limb power; long term—incomplete recovery with compromised sphincter function at discharge; regained mobility with ongoing improvement in lower limb power
Case 4: Westmead Hospital, Sydney, 26 y, male HIV uninfected, India[a]	PTB with CNS and bone involvement	Multiple brain and spinal tuberculomas with raised ICP, compressive spinal myelopathy, and cold abscesses	Empiric HRZE, then HR (900 mg) Z + lfx	Before: High-dose steroids for 6 wk with unsuccessful weaning After: High-dose steroids for 2 mo; tapered over 1 mo	10 mg/kg (0, 3 wk) 5 mg/kg (7, 17 wk)	Rapid resolution of fever and neurological improvement (reduced pressure effects); long term—regained sphincter function and mobility with ongoing improvement on rehabilitation

Abbreviations: amk, amikacin; bdq, edaquiline; cfz, clofazimine; CNS, central nervous system; E, ethambutol; H, isoniazid; ICP, intracranial pressure; lfx, levofloxacin; lzd, linezolid; mfx, moxifloxacin; PTB, pulmonary TB; pto, prothionamide; R, rifampicin; TB, tuberculosis; TBM, TB meningitis; Z, pyrazinamide.

[a]Country of origin.

[b]High-dose steroids included intravenous dexamethasone (4–8 mg 3–4x/d) and/or oral prednisone (1–2 mg/kg/d - maximum 60 mg/d).

[c]After identification of pan-resistance to all first-line drugs, including high-level isoniazid and low-level moxifloxacin resistance.

[d]Linezolid (6 months) and amikacin (12 months) stopped after demonstrated toxicity.

[e]Isoniazid replaced by moxifloxacin given high-level isoniazid monoresistance.

tuberculomas seen on MRI. A second dose of infliximab induced another prompt response, and the patient continued to make a slow recovery, receiving a total of 3 monthly doses. Linezolid (after 6 months) and amikacin (after 12 months) were ceased due to bone marrow suppression and sensorineural hearing loss, respectively. In total, the patient completed 24 months of treatment and was discharged to a disability home, where he lives independently with minimal caregiver help.

Case 2

A 32-year-old woman (on TB treatment) presented with a 7-day history of bilateral thigh pain and paraesthesia, gait disturbance, and urinary retention. Spinal MRI revealed compressive lesions at T5 and T11/12, occurring 4 months after commencing treatment for culture-confirmed miliary tuberculosis; CSF was not assessed at the time. Tuberculosis treatment consisted of isoniazid, rifampicin, pyrazinamide, ethambutol (isoniazid discontinued after documented high-level resistance), and moxifloxacin, with excellent treatment adherence and no vomiting or clinical indication of malabsorption, such as diarrhea. High-dose IV dexamethasone was initiated, and an urgent T4-6 and T11-12 laminectomy was performed, which was complicated by dense pachymeningeal adhesions. With new-onset fecal incontinence, further debulking of the T11/12 lesion was performed, but distressing symptoms persisted.

Histopathology from both lesions showed necrotizing granulomas that were negative for acid fast bacilli and mycobacterial growth. In the absence of live bacilli or any documented steroid response, infliximab was started, with rapid clinical improvement. Full bowel and bladder control, as well as mobility, was regained within 2 weeks. In the absence of raised inflammatory markers, serial positron emission tomography (PET) scans were used to track treatment response with significant reduction in glucose uptake at 2 months and no ongoing activity detected at 4 months, when infliximab treatment was stopped.

Case 3

A 53-year-old woman visiting from Indonesia presented with paraplegia, fecal incontinence, and urinary retention, as well as headache and a third cranial nerve palsy. Extensive intracranial and intraspinal leptomeningeal and pachymeningeal enhancement was demonstrated on MRI. Her CSF grew a fully susceptible strain of *Mycobacterium tuberculosis*. Therapy with isoniazid, rifampicin, pyrazinamide, and moxifloxacin together with high-dose steroids led to initial improvement with resolution of headaches and the third nerve palsy, but after 7 weeks of treatment and while still on high-dose steroids, the patient experienced worsening headaches and new-onset vomiting. Repeat MRI demonstrated increased leptomeningeal inflammation with multiple new intracranial and intraspinal tuberculomas (Figures 1 and 2).

Treatment with infliximab resulted in rapid clinical improvement. Fever and headaches briefly recurred before the second monthly dose, with a total of 3 monthly doses administered. High-dose oral steroids were continued for 4 months before slow tapering. Thalidomide and lenalidomide were trialed for longer-term inflammatory suppression, but both resulted in an extensive generalized rash and were discontinued. A progress MRI demonstrated significant improvement in leptomeningeal enhancement and ring-enhancing tuberculomas after 6 months of therapy. The patient returned to Indonesia 8 months after treatment initiation, having regained muscle strength, but sphincter function remained compromised.

Case 4

A 26-year-old male student from India was admitted with cough, weight loss, and lethargy. There were multiple lung cavities on chest computed tomography (CT), but he had no neurological signs and a noncontrast CT scan of the brain detected no intracranial pathology. He commenced treatment on standard first-line therapy without corticosteroids. Within days of treatment initiation, he developed headache, vomiting, and disorientation, with bilateral lower limb weakness and urinary retention. An MRI of the brain and spine demonstrated communicating hydrocephalus with extensive leptomeningeal enhancement involving the spine, as well as multilevel spondylodiscitis with paravertebral abscesses. A lumbar drain was inserted, and high-dose IV dexamethasone was commenced. The rifampicin dose was increased to 900 mg/d, and levofloxacin 750 mg/d was added. *M. tuberculosis* grown from sputum was subsequently shown to be fully drug susceptible.

Six weeks later, while still on IV dexamethasone, the patient developed new fever, worsening leg weakness, and diplopia. MRI of the brain and spine demonstrated increased basal meningeal enhancement, a new left occipital tuberculoma, and evidence of compressive myelopathy with progression of the spondylodiscitis. Fever and neurological symptoms improved rapidly after a dose of infliximab. Following symptom recrudescence, repeat infliximab doses were given 3, 7, and 17 weeks later, each time followed by prompt improvement. Repeat MRI at 6 months demonstrated resolution of the meningitis, hydrocephalus, tuberculomas, and spondylodiscitis with improvement of the paravertebral abscesses, now regarded as too small for drainage. The antibacterial treatment was rationalized to rifampicin and isoniazid with a plan to treat for 12 months in total.

DISCUSSION

All 4 cases experienced clinical deterioration despite adequate antibacterial treatment and high-dose corticosteroids. In every instance, infliximab therapy was followed by rapid clinical improvement; no adverse effects were reported. The pronounced

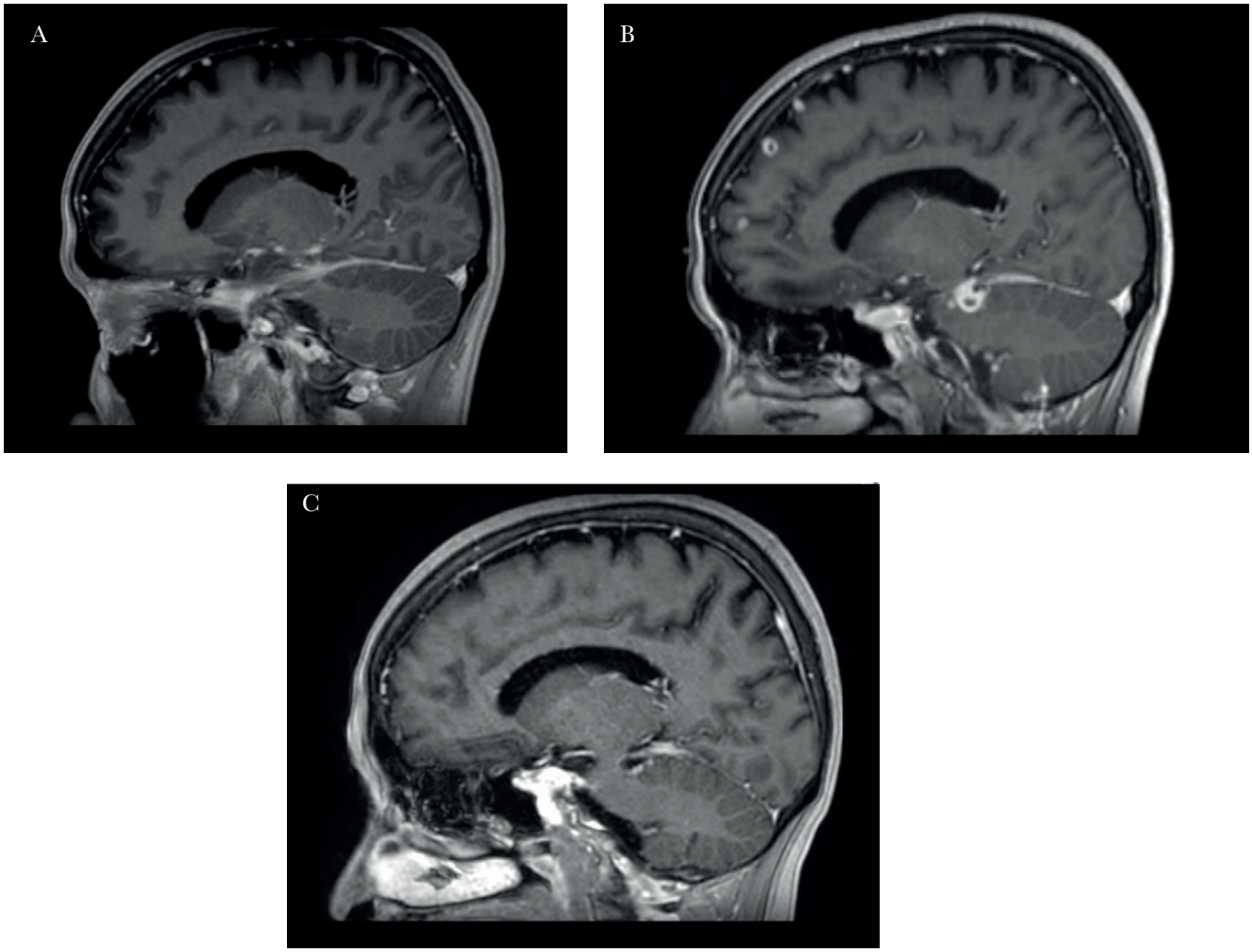

Figure 1. T1-weighted postgadolinium MRI brain images demonstrating evolution of brain tuberculomas in Case 3; pre– and post–infliximab use. MRI of the brain at (A) time of presentation, (B) week 7 post–commencement of TB therapy with formation of multiple tuberculomas (pre-infliximab), and (C) week 21 post–commencement of TB therapy and after 3 doses of infliximab, demonstrating complete resolution of brain tuberculomas. Abbreviations: MRI, magnetic resonance imaging; TB, tuberculosis.

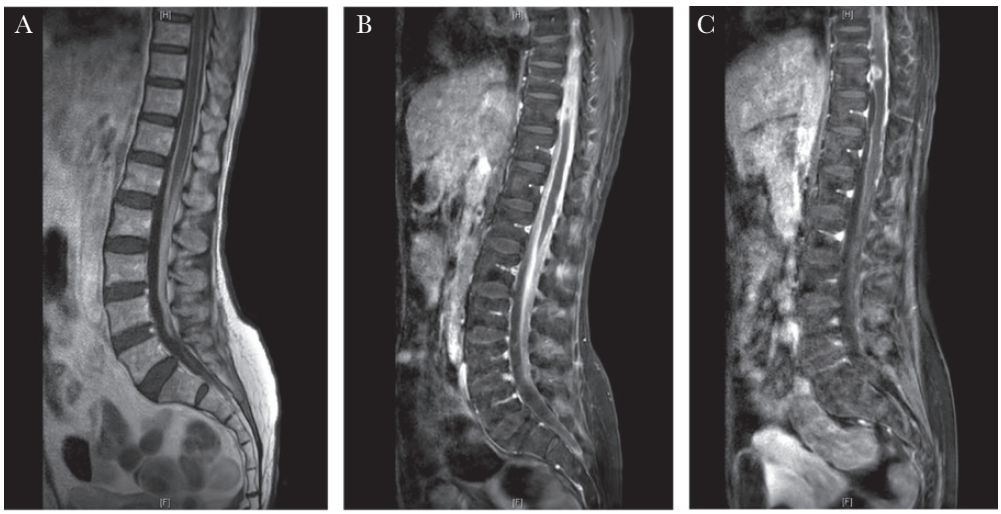

Figure 2. T1-weighted postgadolinium MRI brain images demonstrating evolution of spinal tuberculomas in Case 3; pre– and post–infliximab use. MRI of the spine at (A) time of presentation, (B) week 7 post–commencement of TB therapy with formation of spinal cord tuberculoma (pre-infliximab), and (C) week 21 post–commencement of TB therapy and after 3 doses of infliximab, demonstrating incomplete resolution of spinal cord tuberculoma. Abbreviations: MRI, magnetic resonance imaging; TB, tuberculosis.

and consistent temporal association in clinical improvement, as well as MRI and/or PET changes, suggests a strong therapeutic effect. Our findings support the observation that TNFα is a key driver of inflammation in TB meningitis [11], consistent with the therapeutic effect observed in previous reports [6–10], including those using other TNFα inhibitors, such as adalimumab [12] and thalidomide [3]. Monoclonal antibodies do not usually cross the blood–brain barrier but may do so in the presence of meningeal inflammation and barrier disruption. In rats with hepatic encephalopathy, infliximab significantly reduced neuroinflammation, as demonstrated on immunohistochemistry [13]. In all reported cases, infliximab was only considered after other treatment options were exhausted, but earlier commencement may have prevented some of the invasive procedures and permanent sequelae. It should be emphasized that anti-TNFα treatment should only be contemplated in the presence of effective antibacterial therapy with adequate CSF penetration [14].

The optimal timing and duration of anti-TNFα treatment, as well as the value of corticosteroid co-administration, remains unclear. Symptomatic improvement, inflammatory markers (if raised to begin with), and MRI or PET changes may guide treatment duration; 3–4 doses of infliximab led to significant and durable clinical improvement in all patients. Although optimal dosing and timing of delivery remain uncertain, a rational approach may be to give 5 mg/kg at 0, 2, and 6 weeks (similar to induction dosing recommended for patients with active psoriatic arthritis), with consideration of additional doses at 10–14 weeks guided by the treatment response. This is based on 3 monthly doses provided in the first description of infliximab use in TB meningitis [6] and the fact that our patients experienced "breakthrough symptoms" before the second monthly dose. Therapeutic drug monitoring would be useful to inform dosing schedules [15] but is rarely available and was not performed in our patients. The added value of high-dose corticosteroids is uncertain and requires further evaluation; in reported cases, deterioration occurred under "steroid cover."

Randomized controlled trials to assess the benefit of infliximab use in tuberculous meningitis, in conjunction with effective antibacterial treatment, would be highly informative and might be considered in the following situations: (1) in immune-competent (HIV-uninfected) patients with paradoxical reactions, (2) in TB/HIV-coinfected patients who experience immune reconstitution inflammatory syndrome (IRIS) affecting the central nervous system, and (3) as part of routine care to prevent severe and irreversible sequelae. Multicenter recruitment using standardized methods is preferred [16], although the numbers required to detect a pronounced therapeutic effect, which is the key clinical need, would be relatively small.

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Patient consent. Patients were treated at 4 different hospitals with different case report requirements. All institutional requirements and local ethical standards were met. Written patient consent was provided in all instances, except 1 patient who left Australia. No patient identifiers were disclosed, and all patients/families indicated agreement that relevant clinical information could be shared for academic purposes in order for other patients to benefit from the knowledge gained.

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